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From **JAIDS: Journal of Acquired Immune Deficiency Syndromes** **Packaging PrEP to Prevent HIV: An Integrated Framework to Plan for Pre-exposure Prophylaxis Implementation in Clinical Practice**

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Abstract and Introduction

Introduction

The primary prevention of HIV infection remains a crucial priority; with 2.7 million new HIV infections world wide in 2008, the rate of new infections continues to outpace the rate at which HIV-positive individuals enter treatment.^[1] In recent years, HIV prevention research has focused on a variety of new biomedical strategies for preventing infection, such as male circumcision, vaccines, topical microbicides, and pre-exposure prophylaxis (PrEP) using antiretroviral (ARV) drugs.^[2]

PrEP entails providing HIV-negative individuals with ARV drugs, and it is widely anticipated as one of the most promising new prevention strategies. The PrEP drugs that have been studied to date (ie, tenofovir and emtricitabine) have an established safety profile in HIV-infected individuals, and ongoing trials of oral and topical PrEP among HIV-negative participants are grounded in animal studies,^[3-7] phase I and II trial data in humans,^[8,9] and initial data that did not demonstrate increased sexual risk behaviors among early PrEP trial participants.^[10] Simulation studies have modeled the effects of PrEP among populations in the United States, Africa, and India, forecasting the possibility of substantial reductions in HIV incidence.^[11-14] Surveys, qualitative data, and anecdotal reports from the United States also indicate that some at-risk individuals have already used ARV drugs for HIV prophylaxis, suggesting that this strategy may be acceptable to some target users.^[15-21]

Despite these indications of promise, many have noted that the practical implementation of PrEP is likely to meet stumbling blocks.^[22-27] Although PrEP is a pharmaceutical intervention for preventing infection, using PrEP as a population-level HIV prevention strategy will require a broader conceptualization of this intervention. Mathematical models predicting PrEP's effects suggest that depending on the efficacy of PrEP drugs, PrEP could provide meaningful benefits at the population level; however, PrEP's population-level effectiveness may be offset by low uptake, suboptimal adherence to medications, and increases in HIV risk behavior among PrEP users (risk compensation).^[11-14] To account for these possibilities, a broader conceptualization of PrEP should include not only PrEP drugs, but also nonpharmaceutical elements, including testing and assessment protocols, behavioral interventions, the long-term interactions between PrEP users and health care providers, and monitoring the population-level impacts of PrEP use.

The goal of this commentary is to aid ongoing efforts to plan for implementation in clinical practice by outlining an optimal PrEP implementation package. To maximize the impact of PrEP as an individual-level and population-level HIV prevention strategy, it will be necessary to bundle ARV prophylaxis drugs with a variety of nonpharmaceutical services. Continuing efforts to anticipate PrEP delivery in clinical practice should address demand for these services and the need for integrated care guidelines. This commentary first explains our focus on clinical practice as a venue for PrEP implementation, then offers a 5-part structure for PrEP implementation in clinical settings. This structure is based on a review and synthesis of the published literature related to PrEP, and it emphasizes aspects of PrEP that have previously received little attention. We conclude by enumerating several implications of viewing PrEP as an multicomponent prevention strategy.

Clinical Practice as a Setting for PrEP Implementation

We focus here on clinical practice for several reasons. Although phase I and II study data suggest that PrEP may be benign to HIV-negative users,^[8,9] sustained clinical monitoring will be necessary to identify and treat PrEP-associated side effects,^[23] at least in the early stages of PrEP rollout. Furthermore, because PrEP is likely to be only partially effective,^[9,11–14] continued monitoring and laboratory testing will also be necessary for the early identification of both wild-type and drug-resistant variants of HIV infection in PrEP users.^[23] Given the need for this ongoing clinical monitoring and laboratory support, clinical practice is among the most feasible implementation settings for PrEP.

Despite the logic of focusing on clinical practice settings at this stage, it is important to note that many individuals at high risk for HIV infection do not access regular clinical care.^[28,29] As guidelines to support PrEP implementation are developed, it will be important to investigate alternative implementation arrangements to reach this underserved group. PrEP users will generally be uninfected, at least at the start of PrEP use, and the ratio of clinical concerns (eg, PrEP prescription, treating side effects, HIV testing) to nonclinical concerns (eg, adherence counseling, behavioral intervention to minimize risk compensation) may allow for some task-shifting from clinical to nonclinical providers. Nonclinical personnel, such as service providers in community-based organizations focusing on HIV prevention, sexually transmitted infection (STI) treatment, and drug abuse, may be well-suited to deliver the sustained behavioral counseling needed to promote optimal PrEP use. This may present opportunities for alternative models of PrEP delivery and collaboration among clinical and nonclinical providers, following models such as the delivery of methadone and suboxone during counseling for drug addiction or the implementation of long-term risk-reduction counseling following the treatment of sexually transmitted infections. The extent to which tasks can be shared among nonclinical and clinical providers will be an important issue to clarify as PrEP is rolled out; although this commentary cannot examine all practice settings in detail, we suggest that the central components of PrEP implementation we identify will remain constant across delivery models.

It is also important to acknowledge variation across clinical practice settings and the populations they serve. The specific challenges of implementing PrEP will likely differ depending on the type of clinical practice, and logical settings for PrEP rollout may include private practice, ARV clinics, emergency rooms (eg, for sexual assault survivors or repeat users of postexposure prophylaxis), voluntary counseling and testing centers (especially those serving couples who are serodiscordant for HIV infection), STI clinics, and community health clinics. As we recognize the diversity of the AIDS epidemic, particularly in international settings (eg, the growing recognition of the epidemic among MSM in resource-limited countries^[30]), community-based clinics serving specific populations may also be promising settings for PrEP implementation. The clinical infrastructure that has been developed to treat HIV, including infrastructure developments funded by global health initiatives,^[31–34] may also be harnessed for PrEP delivery. Specific challenges that may vary among practice settings could include identifying those who may benefit most for PrEP in private practice settings, incorporating sustained behavioral counseling in settings where clinicians have limited time with patients, working with patients without insurance or other means of paying for PrEP in community-based health clinics and other practices serving low-income patients, and striking a balance between treatment and prevention in settings such as emergency rooms, STI clinics, and clinics serving serodiscordant couples.

Implementation challenges will also vary across clinical practices depending on the character of the local HIV epidemic (generalized or localized) and the economic environment (high-income, middle-income, or resource-limited country). In high-income or middle-income countries with localized epidemics, specific challenges may include securing insurance coverage for PrEP, formulating guidelines to regulate access to PrEP, and delivering services in a way that is accessible to underserved populations. In resource-limited settings with generalized epidemics, additional implementation challenges may include heightened financial constraints for purchasing PrEP drugs and supporting services, concerns that cheaper behavioral means are available for preventing HIV infection, the relative scarcity of clinicians, the need to identify and serve the most marginalized populations, the need for further infrastructure improvements to support PrEP implementation and population-level monitoring, and tensions caused by the use of ARVs for prophylaxis when the coverage of ARVs for treating people living with HIV remains incomplete. Again, we lack the scope here to examine each of these settings in detail, but we suggest that PrEP implementation in each setting will require both pharmaceutical and nonpharmaceutical components, and that policymakers anticipating PrEP rollout should anticipate demand for a variety of services to support PrEP use.

Optimizing PrEP Through a Multicomponent Package

For the individual health care consumer using PrEP, an optimal package will include 4 complementary components: PrEP drugs, safety monitoring, behavioral intervention, and the integration of PrEP as part of a comprehensive care platform. To support the use of PrEP as a population-level prevention strategy, we also include a fifth component, the monitoring of population-level effects such as the incidence of wild type and drug-resistant HIV. Although this overall framework is unique to PrEP, it raises issues that may also apply to other biomedical interventions for HIV prevention (eg, circumcision).

Component 1: Pharmaceutical Intervention

The prescription, delivery, and administration of PrEP drugs is the central focus of PrEP implementation. The scale-up of ARV treatments for HIV infection has illuminated challenges in delivering pharmaceutical interventions. Some of these challenges, which are heightened in low-income settings, have included training and retaining sufficient numbers of health workers; ensuring the availability of health care in rural settings; establishing and maintaining clinical, laboratory, and public health infrastructure; financing sustained access to drugs, care, and supplies; serving areas with high demand; overcoming barriers to accessing care such as stigma, lack of awareness, and geographical distance; providing ARV care to children; implementing appropriate monitoring and evaluation systems; sustaining patient adherence; and managing drug-related toxicity and resistant infections.^[35,36] Several of these challenges, such as serving areas with high demand and sustaining patient adherence, may be even greater for PrEP, given that the drugs are preventive and intended for currently healthy individuals. PrEP may also pose additional challenges, such as securing financing for PrEP drugs when financially cheaper alternatives for HIV prevention (eg, condom use) exist.

Ongoing trials and additional studies are necessary to develop guidelines for PrEP eligibility, optimal PrEP dosing, necessary adherence, route of administration (topical or oral), and channels for PrEP prescription and monitoring. As data become available, guidelines and algorithms for optimal use will be vital for large-scale implementation. Strategies for implementing access to PrEP must be titrated to setting-specific characteristics, such as drug supply and local safety regulations, drug financing mechanisms, pharmacy structures, procedures for prescription by clinicians (who are subject to licensing and education regulations), and dissemination channels for practice guidelines. As we have learned from the implementation of ARV treatment,^[35] successful decision-making and the subsequent implementation of PrEP may require contributions from a range of stakeholders, including national ministries of health, donors, civil societies, activist organizations, representatives of vulnerable groups, clinical and nonclinical service providers, and international organizations (such as United Nations agencies and the World Health Organization), alongside scientific experts in PrEP efficacy, toxicity, and effectiveness. Issues of PrEP drug financing, supply, and regulation may be especially challenging in countries that already experience heavy burdens of treating HIV and AIDS-related illness.

Component 2: Safety Screening

Consistent with guidelines for testing members of high-risk groups at least annually for HIV,^[37] repeated testing at regular intervals will be recommended as part of the PrEP care platform. To address the risk of new HIV infection, including the acquisition of drug-resistant HIV and the development of secondary resistance in PrEP users,^[23] repeated and frequent HIV testing is an essential component of safe PrEP use. Uncertainty about the necessary rate of testing is an important question bearing on PrEP's feasibility, and a high frequency may be necessary to minimize the risks of secondary resistance. Implementing these tests will entail laboratory costs, possible infrastructure expansion,^[24,38] and in some cases, coordination among clinic-based, community-based, and home testing mechanisms. Importantly, PrEP may only be cost effective for individuals above a certain level of HIV risk.^[11] Assessments of PrEP eligibility will, therefore, be integral to implementation. Once guidelines have specified which individuals should receive PrEP (eg, according to demographic, regional, clinical, and/or behavioral characteristics), assessment protocols will be necessary to identify potential PrEP users, to ensure that current PrEP users still qualify, and to recommend discontinuation of PrEP when it is no longer indicated for an individual user.

Experience with the use of tenofovir and emtricitabine by HIV-infected individuals has indicated that side effects, such as loss of bone density or aggravation of renal impairments, although uncommon, will require ongoing clinical and laboratory monitoring.^[24] In addition to initial and routine tests of renal function, at-risk PrEP users will likely need to be screened for hepatitis B and other sexually transmitted infections regularly. Like all medical tests, these assessments will be subject to regulations that ensure quality, appropriate frequency and types of testing, laboratory standards, qualifications of testing personnel, and established channels for clinical guidelines. The feasibility and costs of repeated HIV screening and other tests for PrEP users in the developing world will also influence the success of PrEP implementation at the population level.

Component 3: Behavioral Intervention

The effectiveness of PrEP as an individual-level and population-level HIV prevention strategy depends on the following three behaviors among PrEP users: PrEP initiation (uptake), adherence, and minimizing HIV risk behaviors. Each of these behaviors is modifiable and potentially responsive to intervention, presenting an opportunity to increase PrEP's effectiveness through clinical counseling and tailored public health strategies.

PrEP initiation will involve engaging at-risk individuals whose behavior would warrant the use of PrEP drugs, counseling them on the benefits and potential risks of PrEP, and gaining their commitment to begin a PrEP regime. As PrEP eligibility guidelines develop, initial outreach efforts might generally target members of known high-risk groups, such as those currently represented in ongoing PrEP trials:^[39] sex workers, high-risk men who have sex with men, HIV-negative individuals in serodiscordant sexual partnerships, and high-risk injection drug users. Community education campaigns will be necessary to educate at-risk individuals about PrEP drugs; however, to avoid misconceptions, education campaigns may need to balance positive messages about PrEP with the realistic acknowledgement that PrEP is only partially effective for preventing HIV. Striking an appropriate balance may be difficult, and it will be

essential to evaluate PrEP education strategies. Measurable outcomes for PrEP education strategies may include rates of PrEP uptake, levels of medication adherence among PrEP users, and ongoing HIV risk behaviors of PrEP users and their sexual partners. As with behavioral interventions for HIV prevention, designs for evaluating PrEP education campaigns may include randomized trials, with assignment at the level of the individual PrEP user (or potential user), groups of PrEP users (or potential users), or by geographical unit for interventions targeting entire communities.

Users' adherence to PrEP dosing schedules will be an integral factor in PrEP's effectiveness, and ongoing and future trials of PrEP efficacy and effectiveness will clarify the optimal dosage schedule. Many current PrEP trials require daily administration, whereas some protocols are experimenting with less frequent dosage, either coitally dependent or on a fixed intermittent schedule. Studies of other preventive or treatment medications (eg, oral contraceptives, antibiotics, ARV therapy) have illustrated the need for interventions to help users incorporate medication dosage into daily routines.^[40–42] Various interventions may promote adherence among PrEP users, including cognitive behavioral skills training, electronic reminders, and social support programs.^[43,44]

Averting increases in risk behavior among PrEP users will also be essential for maintaining PrEP's protective effects. A prominent concern in the PrEP literature is the potential for risk compensation—the phenomenon whereby individuals receiving PrEP might increase HIV-related risk behaviors on the assumption that they are protected against HIV infection.^[10,45,46] Some models have suggested that even small increases in risk behavior could offset or reverse PrEP's protective benefits at the population level.^[13,14] Efforts to minimize risk compensation must be incorporated in clinical counseling and community education campaigns, and protocols for following up PrEP users should incorporate risk reduction counseling and ongoing assessments of behavioral risk-taking. For example, an individual-level strategy may be administering a behavioral risk assessment to PrEP users before each regularly scheduled HIV test and providing each user with personalized feedback on changes in risk behavior since his or her previous test. Population-level educational messages for PrEP users could be delivered alongside existing HIV prevention messages for at-risk groups, emphasizing the need for both PrEP users and nonusers to engage in safer behaviors. If PrEP eligibility guidelines include behavioral indicators, these guidelines should also clarify the relationship between behavioral risk reduction and continued eligibility for PrEP drugs.

Two general concerns cut across these behavioral components. One concern is creating a framework to ensure that behavioral intervention accompanies PrEP prescriptions, especially since behavioral interventions may be less amenable to regulation and guidelines than protocols for PrEP prescription or ongoing HIV testing. A second concern is the burden on service providers to assess behavioral risks and provide necessary behavioral intervention, which may present opportunities for task shifting and collaboration between clinical and nonclinical personnel. Protocols to incorporate behavioral assessment and counseling in the overall PrEP package might involve trained health service staff such as nurses, social workers, or paraprofessionals; these protocols might also allow for collaborations with community-based organizations with expertise in outreach and behavioral risk reduction. Where behavioral services are delivered in clinical practice, it is important to consider the resource implications of training staff to perform this role and the additional patient-provider time that will be needed to provide adequate counseling in the clinical setting.

Component 4: Integration of PrEP as Part of Comprehensive Care

Because PrEP implementation requires clinical assessment, prescription, routine testing, and long-term (even if infrequent) monitoring of PrEP users, it will require a relatively stable interface of contacts between PrEP users and clinical providers. Individuals who are at highest risk of HIV infection, and who therefore may qualify for PrEP, are likely to come from underserved populations with other healthcare needs.^[28–29] For example, they may present with sexually transmitted infections, pregnancy, substance abuse or addiction, mental health issues, malnutrition, or other conditions that are prevalent in their community, ranging from endemic infections like malaria to previously unaddressed chronic medical conditions. The need for PrEP users to have regular clinical contact can provide access points for additional screening and health care services tailored to population-specific needs. The long-term care relationship will include the detection and treatment of PrEP-associated side effects and treatment of newly acquired wild type and resistant HIV infection. The clinical need to engage at-risk individuals who qualify for PrEP can also give rise to opportunities or obligations to address unrelated health needs that might at first seem distant from HIV risk. It is also important to note that, in the long run, PrEP is intended to increase the longevity of PrEP users, and thus may require the expansion of services to meet their long-term needs, as is currently witnessed with an aging HIV-positive population due to improvements in ARV outcomes.

The need for integrated care is a natural consequence of the probable long-term duration of PrEP, as users will need to adhere to PrEP regimens regularly during periods of HIV risk. Although clinicians may intuitively understand that a long-term prescription and routine testing create an interface for care, this aspect of PrEP has been rarely discussed in the public health literature to date. It may be difficult to anticipate all of the implications of this long-term care relationship before scaling up PrEP. However, the PrEP care relationship is an opportunity to do more for PrEP users, and PrEP users may choose to build on these contacts to seek more services. This aspect of the overall PrEP package may lead to unexpected costs and systemic health care needs if we do not anticipate and prepare for it appropriately.

Component 5: Monitoring PrEP's Population-level Impact

The effective use of PrEP as a population-level HIV prevention strategy will depend not only on drug efficacy and the behaviors of PrEP users but also on the development and spread of drug-resistant HIV. National monitoring and evaluation systems are necessary to assess the net benefits of PrEP use at a population level and to provide the feedback needed to fine-tune guidelines for delivering PrEP to individual users. These monitoring systems should at minimum assess the incidence of wild type and resistant HIV infection among PrEP users and the overall incidence of infection in the general population. Beyond these data, monitoring systems should assess the uptake or coverage of PrEP in at-risk groups, which will help estimate the number of potential infections averted due to PrEP use. To the extent possible, systems could also incorporate available data on individual adherence levels (eg, prescription refills), risk compensation behavior coupled with suboptimal adherence, the rate at which individual PrEP users return for scheduled HIV testing, and data on expenditures associated with PrEP use and the treatment of PrEP-related side effects. Overall, this monitoring and evaluation is critical to identify whether the net effect of PrEP is beneficial at the population level. Depending on population-level impacts, it may be necessary to adjust PrEP implementation protocols to increase the frequency of HIV testing, expand outreach to promote greater uptake of PrEP, or intensify behavioral interventions that support adherence and minimize risk compensation activity among PrEP users.

Conclusions

This Commentary has proposed a 5-part structure for optimizing PrEP implementation in clinical practice. The HIV prevention literature reflects a keen awareness that PrEP will require support services, and including these services in a unified implementation framework can help to organize these discussions. We believe that taking an expanded view of PrEP—including an optimal package of PrEP prescription, safety screening, behavioral intervention, integration of PrEP with other healthcare services, and population-level monitoring—will help clinicians and policymakers prepare more effectively for implementation.

The balance of these 5 components will likely shift as we learn more about PrEP's actual efficacy and effectiveness. Although initial animal studies and data from phase I and II studies in humans offer reason for optimism about PrEP's efficacy for HIV prevention, the actual protective benefits of PrEP remain uncertain. If PrEP is not highly efficacious, the need for continuing behavioral intervention will take on greater significance, as optimal behaviors will be necessary for users to benefit from PrEP's partial protective effect. If PrEP has low efficacy, future studies should emphasize the development of interventions to maximize medication adherence and minimize risk compensation behavior (both of which will be necessary to limit PrEP failures), and monitoring and evaluation systems to assess PrEP failures and the incidence of drug-resistant HIV will be especially important. If PrEP proves to be highly effective in some, but not all populations, more focused recommendations for PrEP use may be needed. Finally, if PrEP has high toxicity among some or all users, the demands of ongoing clinical monitoring and testing may increase, altering the balance of clinical and nonclinical service needs. This balance may in turn influence the types of delivery arrangements that may support effective PrEP implementation, requiring proportionally more involvement by clinical providers.

Viewing PrEP as an integrated implementation package can also help to identify features of the package as a whole. Although a full discussion of these implications is beyond the scope of this review, several characteristics are noteworthy. First, delivering the optimal PrEP package will involve a multidisciplinary cast of providers, including clinicians, HIV testing counselors, laboratory staff, behavioral interventionists, and other health services personnel depending on how PrEP is integrated into comprehensive care. Second, different components of PrEP are subject to different types of regulation, which may present problems for scaling up an integrated PrEP package. For example, although it may be possible to shape PrEP drug prescriptions and testing regimes through clinical guidelines, it may be much more difficult to shape behavioral interventions in a centralized way. Furthermore, although PrEP drug dosages and testing regimes may be similar across PrEP users, behavioral risk factors and underserved health needs may vary more widely. This suggests that more local tailoring will be necessary for behavioral intervention and integrating PrEP into comprehensive care, and maintaining the integrity of an optimal PrEP implementation structure may be a formidable challenge. Third, the specific content of the PrEP package may shift over time due to evolution in behaviors, social and clinical contexts, risk-reduction strategies, and the virus itself. This evolution highlights the importance of population-level monitoring and adjustment of PrEP protocols. Fourth, discussions about PrEP scale-up suggest that the HIV prevention field should cultivate a method for thinking systematically about implementation concerns, especially for scaling up an intervention package with pharmaceutical, diagnostic, behavioral, and clinical components. Given the rapid progress in research on biomedical prevention strategies, PrEP is neither the first nor last hybrid intervention for preventing HIV. A taxonomy of implementation challenges should be a focus of future inquiry.

Finally, this 5-part framework points to some ways that clinical and nonclinical service providers can prepare to take on new roles in PrEP implementation. If PrEP is approved for use, it may change the way in which both HIV prevention and treatment services are delivered. Because PrEP may only be cost effective for individuals at a high level of HIV risk, and especially given the potential for risk compensation, clinical providers in all practice settings may need to become more comfortable asking questions about patients' specific HIV risk behaviors, including sexual behaviors and

drug use. Clinicians who treat HIV-positive individuals can play an integral role in PrEP implementation, in part by asking new questions about the sexual partners and drug-use partners of their HIV-positive patients, and they should prepare to incorporate these types of questions into routine practice. Nonclinical providers of HIV prevention services (eg, community-based organizations) will play a crucial role in outreach and education to inform at-risk individuals about PrEP, particularly those who do not access medical care consistently. Strengthening outreach practices should therefore be a priority. To inform potential consumers effectively, these service providers will also need to seek education on PrEP's costs, benefits, possible side effects, and associated demands for ongoing medication adherence and HIV testing. Policymakers planning for PrEP implementation may consult models of long-term service delivery that involve a division of tasks among clinical and nonclinical personnel, such as the models for long-term drug abuse treatment and STI treatment as identified above. Policymakers should also be attentive to the challenges that have arisen during the implementation of ARVs for treating HIV infection, as many of these same challenges are likely to accompany the use of ARVs for prevention.

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